eAppendix. Supplementary Information

Table of Contents

TACT investigators, leadership, and trial committees

In addition to the authors the following Investigators and Coordinators participated in the Trial to Assess Chelation Therapy.

United States

Bronx-Lebanon Hospital Center- Bhalodkar, Narendra, Noneta Montinola; Magaziner Center for Wellness- Allan Magaziner, Betty Ann Persico; The Ohio State University Medical Center- Raymond Magorien, Luba Mazanec; The Johns Hopkins University- Pamela Ouyang, Jeanne Wingo; Baystate Medical Center-Mara Slawsky, Judith Fleurent; Heart Care Center- Russell Silverman, Sherri Loucks; Androscoggin Cardiology Associates- Robert Weiss, Diana Cass; Family Health Medical Services- Robert Berke, Paige Davidson; Main Line Health Heart Center- Robert Bulgarelli, Susan Herring; New York VA, Cardiovascular Clinical Research Center-Steven Sedlis, Estelita Anteola; University Hospitals of Cleveland- Austin Halle, Lian Yang; The Institute of Integrative Medicine- Majid Ali, Mahboobullah Baig; Deborah Heart and Lung Center- Alexander Poulathas, Linda Dewey; New York University, School of Medicine-Harmony Reynolds, Chao Wang; Rhinebeck Health Center- Kenneth Bock, Debbie Truin; Schachter Center for Complementary Medicine- Michael Schachter, Sally Minniefield; Dr. Yulius Poplyansky- Yulius Poplyansky, Marjorie Patino; Stockton Family Practice- Stuart Freedenfeld, Verna Good; Hudson Valley Heart Center- Glenn Gerber, Patricia O'Brien; Celebration of Health Association- Terry Chappell, Marcia Arnold; Wholistic Health Center-Ralph Miranda, Barb Casella; Staten Island Heart- James Lafferty, Lenora Tafuri-Acevedo; Marino Center for Integrative Medicine- Guy Pugh, Vivian Cole; Land Clinical Studies-James Garofalo, Krystle Chavez; Comprehensive Heart Care- James Roberts, Debra Braun; Advanced Family Medicine- James Johnson, Rosemary Stevenson; Longevity Medical , PA- Ivan Krohn, Lewis S. Korb, Lake Cable Medical Center- Jack Slingluff, John Mountford; Woodlands Healing Research- Robert Schmidt, Evelyn Alentin; Matrix Clinic-Lisa Lichota, Keith Rost; Maine Integrative Wellness- Sean McCloy; Upper Valley Family Care- Richard Plumb, Lynn Shough; Arkansas Center for Physical Medicine and Rehabilitation- Linda Bunch, April Archey; Riverside Family Medical- Lisa Merritt, Lisa Lockett; Florida Cardiovascular Group-Steven Borzak, Dina Herig; University of Arkansas for Medical Sciences-Joseph Bissett, Sandra McLaren; Central Arkansas Veterans Healthcare System- Joseph Bissett, Sharon Locke; The Heart Group- Joseph O'Bryan, Mary Barr; Boice Willis Clinic- Shalendra Varma; Cardiology Consultants of South Florida- Ricky Schneider, Rochelle Mckenzie; Complementary Medical Services- James Carter, Kaylynn LeBlanc; Athens Surgery Clinic- Joseph Holliday, Vivian Holliday; Biogenesis Medical Center- Theodore Rozema, Dolly Corbin; Mount Sinai Medical Center- Robert Ciccia-Maclean, Pablo Guala; Mount Sinai Medical Center of Florida- Todd Heimowitz, Helen Garcia; Caring Cardiology- Roy Heilbron, Celia Heilbron; Pain and Healing Center- Angelique

Hart; Baptist Cardiac and Vascular Institute- Barry Katzen, Ivette Cruz; Advantage Health Center, LLC- Donald Tice; Wellness and Longevity Center of Louisiana- Sangeeta Shah, Debbie Vige; Virginia Beach General Hospital- John Griffin, Pam Hollsten; Jack Young, MD - Jack Young, Estela Fransbergen; Tru Med- Rajiv Chandra, Terry Murphy; Mark O'Neil Speight, MD- Mark Speight, Janine Speight; Grace Medical Association- Smart Idemudia, Geneve Gutierrez; The Cardiovascular Group- Lawrence Miller, Deanna Overbeck; Heart and Vascular Center for Research, Inc.- Clayton Bredlau, Amy Heineman; The Blend Institute- Timothy Blend, Helena Williams; Innovative Research of West Florida- Miguel Trevino, Kimberly Mai; Wellness Center- Jose Oblena, Bonita Harris; Chelation Centers of Texas- Dorothy Merritt, Elizabeth Collins; Tyler Total Wellness Center- Pieter deWet, Cindy deWet; Jenks Health Team- Gerald Wootan, Susan Shaw; Integrative Medical Associates- Connie Ross, Michelle Simpson; COR Research- Clinton Corder, Clinton, Michael Stout; Wright Health & Wellness Center- Robert Wright, Alma Steffen; Florida Cardiovascular Institute- John Sullebarger, Leona Stewart; Wellness Works- Carol Roberts, Berni McClendon; Life Family Practice Center for Complementary and Alternative Medicine- Nelzon Kraucak, Mariann Haring; Northeast LA Anti-Aging and Wellness Center- Linda Bunch, Shauna Gallien; Tequesta Family Practice- R.J. Oenbrink, Joe Militello; Full Circle Medical Center- Charles Adams, Jackie Miles; Family/ Complimentary Medicine- Karen Dantin, Laurie McDuff; White-Wilson Medical Center, P.A.- Leslie Fleischer, Cheri Penas; Pearsall Medical and Bariatrics- Gurney Fields Pearsall, Marina M Pearsall; Mueller Institute For Functional Medicine & Research- Jeffrey Mueller, Jeffrey, B. J. West; Louisiana Anti-Aging & Wellness Care- Linda Bunch, Kim Robinson; Hillsboro Family Medicine- Paul Kotturan, Nalini Reddy; The Castle Clinic, PLLC- Robert C. Allen, Laura Whitaker; Heart Specialists- Rajinder Bhalla, Teresa Hicks; Florida Medical Clinic, P.A- Hector Fontanet, Precious Hoyle; Hyperbaric Medicine Inc.-Albert Zant, Michelle Potpan; University of Missouri Health Care- Greg Flaker, Sharon Clasby; Henry Ford Health System- Jonathan Ehrman, Matthew Saval; University of Kansas Medical Center- Jeanne Drisko, Elizabeth Schrick; Waters Preventive Medical Center- Robert Waters, Sarah B. Chapman; Bircher Chiropractic and Wellness Center- Donald Riemer, Laura Sembach; Preventive Medicine- Varsha Rathod, Heather Moran; Born Preventive Health Care Clinic & Crossroads Healing Arts- Tammy Born, Judy Schneider; Integrative Medicine Center at Schneck Medical Center- Steven Windley, Stephanie Pyle; Mayo Clinic and Foundation Cardiovascular Health Clinic- Gerald Gau, Dawn Shelstad; Berman Center for Outcomes and Clinical Research- Richard Grimm, Mary Perron; Parchment Family Practice- Eric Born, Julie Ladkrood; The Preventive Medicine Center- Kenneth Ganapini, Venus Barney; West Holt Medical Clinic- Robert Randall, Teresa Kohle; Northwest Indiana Cardiovascular Physicians Inc.- Hector Marchand, Cheryl Kwiatkowski; Cardiovascular Research Foundation- Anita Arnold, Dana Kappel; Care Foundation Inc- Timothy Logeman, Karen Olson; The Center for the Improvement of Human Functioning International- Ron Hunninghake, Mavis Schultz; Brian Dieterle MD, PhD, Internal Medicine-Brian

Dieterle, Debra Louderback; Marjon Fariba- Marjon Fariba, Sepideh Arvin Matthew; Hope Medical Holistic Clinic- Zbigniew Grudzien, Marinela Matei; Coyote Healing Center Integrative Medicine and Psychiatry- Richard Dexter, Christine Rupley; ACT/Cardiovascular Research Institute- Ronald Karlsberg, Tracey S. Gerez; Patrick A Golden-Patrick Golden, Kathy Sasser; Aurora Denver Cardiology Associates- Nampalli Vijay, Melinda Washam; Casdorph Clinic- Richard Casdorph, Heather Browning; Chris Hatlestad,MD, PC- Chris Hatlestad, Christine Ohlemann; Alaska Cardiovascular Research Foundation- Paul Peterson, Lori Heaney; Scripps Center for Integrative Medicine- Erminia Guarneri, Eva Stuart; Frontier Medical Institute- Terry Grossman, Kathryn Bottinell; Cardiac Solutions- Vishal Patel, Denise Wells; Freedom Center for Advanced Medicine- William David Voss, Lorna Gordon; Gordon Medical Associates- Eric Gordon, Win Bertrand; Phoenix Wellness Group- Eleanor Hynote, Katie Lacey; The Center for Optimal Health- Ann McCombs, Arlene Sellereite; Center for Environmental Medicine- Chris Hatlestad, Cambor Wade; St. Charles Health System- Bruce McLellan, Noura Sall.

Canada
Seekers Centre for Integrative Medicine- Richard Nahas (Country Leader), Shadi Nahas; Anti-Aging & Family Wellness Clinic- Arun Dosaj, Diane Dosaj; Chelox- Shmuel Bergman, Mary Toro; The Wellness Centre- Ben Boucher, Robyn Whitty; Jaconello Health Centre- Paul Jaconello, Hildegard Beath; Markham Integrative Medicine- John Gannage, Tony Estacio; Chelation & Natural Therapy, Chelation Center of Don Valley Inc, Chelation Center of Barrie, Inc- Fred Hui, Eva Pacaba; Saskatoon Chelation Centre- Edward Nykiforuk, Val Kalyn; Dr. Clare Minielly- Clare Minielly; Recherche Cardiologie Hôtel-Dieu du CHUM- François Reeves; North Bay Complementary- Jean Aubry, Barbara Brooks; Montreal Heart Institute- Jean-Claude Tardif, Randa Zamrini; Cline Medical Centre- John Cline, Frank Pluta.

Data and Safety Monitoring Board: Howard Hodis (Chair), Steven Buckley, Barry R. Davis, Theodore Ganiats, Gail Geller, Robert Nash, George Wyse.

Committees and Coordinating Centers.
Clinical Events Committee at the Brigham & Women's Hospital: Marc Pfeffer, Eldrin Lewis, Chau Duong, Renée Mercier.

Data Coordinating Center at the Duke Clinical Research Institute, Durham, NC: Kerry Lee (Principal Investigator), Sandra Tourt-Uhlig, Joyce Good, Lauren Lindblad, Loren Lytle, Vivian Thompson, Linda Szczech, Gerard Esposito, Meredith Smith, Trevorlyn Haddock, Constance Bardinelli, Wanda Parker, Lindsey Lambe, Cresha Cianciolo, Brian Fox, Emlie Johnson, Mary Molina, Rita Weber, Leslie Williams.

Economics and Quality of Life Coordinating Center Data Coordinating Center at the Duke Clinical Research Institute, Durham, NC: Daniel Mark (Principal Investigator), Nancy Clapp-Channing, Diane Minshall- Liu, Jason Blevins, Kevin Anstrom, David Knight, Thomas Redick, Andrea Davis, Miguel Pena.

Clinical Coordinating Center at Mount Sinai Medical Center, Miami Beach, FL: Gervasio Lamas (Principal Investigator), Ana Mon, Esteban Escolar, Steven Hussein, Pablo Guala, Kayvan Amini, Faisal Shamshad, Jacqueline Arciniega, Jamie Zimmerman, Danielle Hollar, Beatriz Acevedo, Helen Garcia, Adam Williams, Matthew Shields, Renea Moss, Virginia Martini, Parminder Singh, Jewmaull Reed, Maria Salas, Carlos Zamora, Tristan Edwards, Stephanie Escalante, Laura Davila, Rachel Margolis.

Vitamin Compliance

As reported in the primary manuscript, there were a total of 783 patients (46%) who, during the course of their follow-up in the trial, prematurely discontinued taking the high-dose or placebo vitamins. Of this number, 394 (50.3%) were in the group randomized to receive the active high-dose vitamins, and 389 (49.7%) were in the group randomized to placebo vitamins.

A plot of Kaplan-Meier curves depicting the pattern of vitamin discontinuations by treatment arm as a function of the time from randomization is presented in e-Figure 1, including a log-rank comparison of the two randomized arms with respect to the time to discontinuation.

A summary of the duration of vitamin therapy in the two randomized arms is provided in eTable 1. Overall the median duration of vitamin treatment was 33.4 months (IQR: 12.6, 59.4). Corresponding information for each randomized arm is also provided in eTable 1. The percentage of patients who took the high-dose or placebo vitamins for at least one full year was 75.6% in both randomized arms. Overall 48.4% of the patients took the vitamins for at least three years (46.9% in the active arm, 49.8% in the placebo arm). A tabulation of the reasons for discontinuing the vitamins by treatment arm is provided in eTable 2.

In eTable 3, baseline characteristics of the 783 patients who discontinued the vitamins are compared with corresponding characteristics of the 925 patients enrolled in TACT who did not discontinue vitamin therapy. Other than a higher percentage of female patients and anterior location of the qualifying myocardial infarction among those who prematurely discontinued the vitamins, there are remarkably no other significant differences. Thus, there does not appear to be any major bias in the baseline risk profile of the patients who were compliant throughout their follow-up period compared to those who prematurely discontinued taking the vitamins.

Also of key importance is the fact that among the patients who did prematurely discontinue the vitamins, the baseline characteristics in the two randomized vitamin arms are very comparable (eTable 4). Other than a higher percentage of diabetics among the active arm patients who discontinued the vitamins compared to placebo, the risk profiles of the patients who discontinued the vitamins are very similar between the two randomized arms.

In summary, the following points are relevant in interpreting the results of the trial:

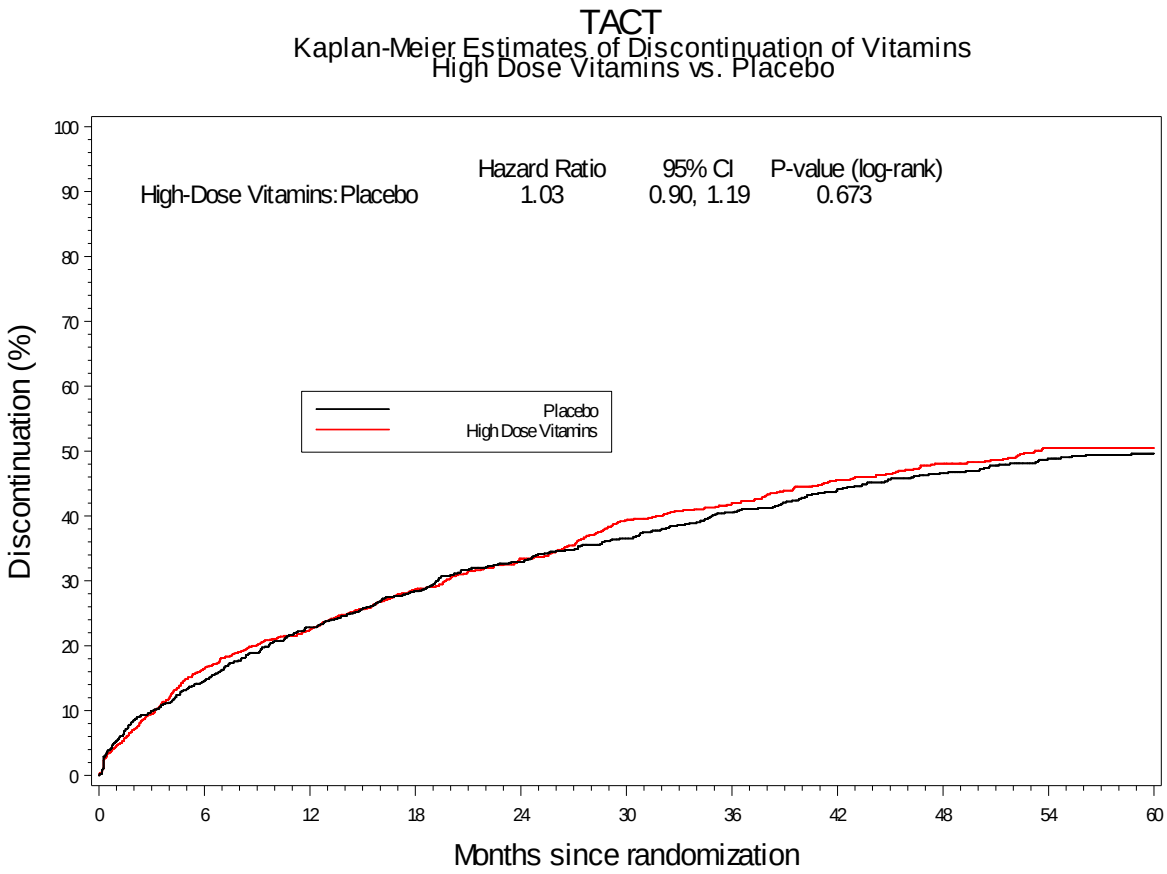
(1) The number of patients in the two randomized vitamin arms who prematurely discontinued taking the vitamins at some point during their

follow-up was nearly identical in the active vitamin arm compared to the placebo arm.

(2) The characteristics of the patients who discontinued taking the vitamins are largely similar to the patients who did not discontinue the vitamins.

(3) Among the patients who did prematurely discontinue the vitamins, the baseline characteristics (other than diabetes) of those in the active arm compared to placebo are well balanced.

e-Figure 1



Number at Risk											
High Dose Vitamins	853	707	645	571	504	433	400	359	320	256	160
Placebo	855	725	646	578	515	463	426	377	332	280	176

eTable 1
Duration of High-Dose/Placebo Vitamin Therapy in TACT

Duration of treatment	**Placebo (N=855)**	**High-Dose Vitamins (N=853)**	**All Patients (N=1708)**
Duration of high-dose or placebo vitamin therapy (months)			
Median (25th, 75th)	35.4 (12.6, 59.5)	31.0 (12.6, 59.2)	33.4 (12.6, 59.4)
Patients who completed at least 1 year of vitamin treatment	646 (75.6%)	645 (75.6%)	1291 (75.6%)
Patients who completed at least 3 years of vitamin treatment	426 (49.8%)	400 (46.9%)	826 (48.4%)
Duration of high-dose or placebo vitamin therapy among those who prematurely discontinued vitamins (months)			
Median (25th, 75th)	13.8 (4.5, 31.4)	13.6 (4.1, 28.6)	13.8 (4.2, 29.4)

eTable 2
Reasons for Vitamin Discontinuation by Vitamin Arm *

	Placebo (N= 855)	High-Dose Vitamins (N= 853)	All Patients (N=1708)	P-value
TOTAL premature discontinuation of treatment (excluding death)	390 (46%)	394 (46%)	784 (46%)	0.67*
Due to adverse event or side effects	31 (7.9%)	39 (9.9%)	70 (8.9%)	0.34**
Patient refusal or noncompliance	304 (78%)	293 (74%)	597 (76%)	0.24**
Physician preference	19 (4.9%)	22 (5.6%)	41 (5.2%)	0.65**
Due to closed site or inability to contact patient	26 (6.7%)	21 (5.3%)	47 (6.0%)	0.43**
Terminal illness or comorbidities	10 (2.6%)	19 (4.8%)	29 (3.7%)	0.094**

* P-value from Log-Rank Test
** P-value from Chi-Square Test

eTable 3
Baseline Characteristics of the Patients Who Did vs. Did Not Prematurely Discontinue High-Dose Vitamins

	Discontinued High-Dose Vitamins (N=784)	Did Not Discontinue High-Dose Vitamins (N=924)	P-value
Demographics			
Age (years)	65.3 (59.2, 72.0)	65.3 (58.9, 71.7)	0.37
Female	156 (20%)	143 (15%)	0.017
Minority (Hispanic or non-Caucasian)	76 (9.7%)	80 (8.7%)	0.46
BMI	29.6 (26.4, 33.5)	29.9 (26.6, 33.7)	0.46
History			
Time from qualifying MI to randomization (years)*	4.6 (1.6, 9.1)	4.6 (1.7, 9.4)	0.95
Anterior MI	329 (42%)	345 (37%)	0.051
Congestive heart failure	154 (20%)	153 (17%)	0.098
Valvular heart disease	84 (11%)	91 (10%)	0.56
Stroke	59 (7.5%)	52 (5.6%)	0.113
Diabetes	262 (33%)	276 (30%)	0.116
Peripheral vascular disease	127 (16%)	141 (15%)	0.61
Hypertension	540 (69%)	629 (68%)	0.72
Hypercholesterolemia	636 (83%)	734 (81%)	0.32
Atrial fibrillation	84 (11%)	111 (12%)	0.41
Former cigarette smoker	450 (57%)	505 (55%)	0.25

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* Median, 25th and 75th percentiles are reported for all continuous variables.

eTable 3
Baseline Characteristics of the Patients Who Did vs. Did Not Prematurely Discontinue High-Dose Vitamins

	Discontinued High-Dose Vitamins (N=784)	Did Not Discontinue High-Dose Vitamins (N=924)	P-value
Coronary revascularization			
CABG	356 (45%)	418 (45%)	0.94
PCI	465 (59%)	542 (59%)	0.78
Either CABG or PCI	647 (83%)	767 (83%)	0.79
Presenting Characteristics			
Blood Pressure			
Systolic	130.0 (118.0, 140.0)	130.0 (120.0, 140.0)	0.25
Diastolic	76.0 (68.0, 80.0)	76.0 (70.0, 80.0)	0.61
NYHA Functional Class			0.65
No heart failure	609 (78%)	740 (80%)	
Class I	101 (13%)	109 (12%)	
Class II	60 (7.7%)	62 (6.7%)	
Class III	14 (1.8%)	13 (1.4%)	
Class IV	0 (0%)	0 (0%)	
Concomitant Medications			
Aspirin	638 (81%)	789 (85%)	0.026
Beta-blocker	554 (71%)	672 (73%)	0.34
Statin	568 (72%)	680 (74%)	0.60
ACE or ARB	496 (63%)	588 (64%)	0.87

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* Median, 25th and 75th percentiles are reported for all continuous variables.

eTable 3
Baseline Characteristics of the Patients Who Did vs. Did Not Prematurely Discontinue High-Dose Vitamins

	Discontinued High-Dose Vitamins (N=784)	Did Not Discontinue High-Dose Vitamins (N=924)	P-value
Clopidogrel	206 (27%)	219 (25%)	0.194
Warfarin	77 (10%)	71 (8.1%)	0.124
Aspirin or warfarin	685 (88%)	817 (89%)	0.48
Aspirin, warfarin or clopidogrel	709 (91%)	843 (92%)	0.54
Diabetes medication			
Insulin	84 (11%)	76 (8.6%)	0.091
Oral hypoglycemic	184 (24%)	196 (22%)	0.33
Multivitamin**	326 (43%)	389 (44%)	0.79
Other vitamins/minerals**	376 (50%)	476 (53%)	0.21
Herbal products	252 (33%)	308 (35%)	0.64
Laboratory Examinations			
Glucose (mg/dL)	103.0 (93.0, 124.0)	102.0 (92.0, 119.0)	0.176
Creatinine (mg/dL)	1.1 (0.9, 1.2)	1.1 (0.9, 1.2)	0.74
Total cholesterol (mg/dL)	166.0 (143.0, 199.0)	163.0 (140.0, 192.0)	0.112
HDL (mg/dL)	43.0 (36.0, 51.0)	43.0 (37.0, 51.0)	0.45
LDL (mg/dL)	91.0 (67.0, 118.0)	87.0 (68.0, 112.0)	0.186
Triglycerides (mg/dL)	143.0 (99.0, 201.0)	137.0 (93.0, 204.0)	0.53

* Median, 25th and 75th percentiles are reported for all continuous variables.
** * Participants were taking at baseline / prior to initiation of the study.

eTable 4
Baseline Characteristics of Patients Who Prematurely Discontinued High-Dose Vitamins by Treatment Group

	Placebo (N=390)	High-Dose Vitamins (N=394)	P-value
Demographics			
Age (years)	65.2 (59.8, 72.0)	65.3 (58.7, 71.9)	0.50
Female	80 (21%)	76 (19%)	0.67
Minority (Hispanic or non-Caucasian)	36 (9.2%)	40 (10%)	0.66
BMI	30.0 (26.6, 33.8)	29.2 (26.1, 33.0)	0.056
History			
Time from qualifying MI to randomization (years)*	4.4 (1.5, 8.7)	4.9 (1.7, 9.5)	0.26
Anterior MI	162 (42%)	167 (42%)	0.81
Congestive heart failure	87 (22%)	67 (17%)	0.062
Valvular heart disease	49 (13%)	35 (9.1%)	0.103
Stroke	30 (7.7%)	29 (7.4%)	0.86
Diabetes	114 (29%)	148 (38%)	0.013
Peripheral vascular disease	65 (17%)	62 (16%)	0.72
Hypertension	269 (69%)	271 (69%)	0.95
Hypercholesterolemia	314 (82%)	322 (83%)	0.60
Atrial fibrillation	48 (13%)	36 (9.4%)	0.154
Former cigarette smoker	213 (55%)	237 (60%)	0.117
Coronary revascularization			
CABG	181 (46%)	175 (44%)	0.58
PCI	235 (60%)	230 (58%)	0.59
Either CABG or PCI	323 (83%)	324 (82%)	0.83

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* Median, 25th and 75th percentiles are reported for all continuous variables.

eTable 4
Baseline Characteristics of Patients Who Prematurely Discontinued High-Dose Vitamins by Treatment Group

	Placebo (N=390)	High-Dose Vitamins (N=394)	P-value
Presenting Characteristics			
Blood Pressure			
Systolic	130.0 (118.0, 140.0)	130.0 (117.0, 140.0)	0.58
Diastolic	75.0 (68.0, 80.0)	76.0 (68.0, 81.0)	0.46
NYHA Functional Class			0.59
No heart failure	299 (77%)	310 (79%)	
Class I	49 (13%)	52 (13%)	
Class II	35 (9.0%)	25 (6.3%)	
Class III	7 (1.8%)	7 (1.8%)	
Class IV	0 (0%)	0 (0%)	
Concomitant Medications			
Aspirin	304 (78%)	334 (85%)	0.014
Beta-blocker	284 (73%)	270 (69%)	0.187
Statin	281 (72%)	287 (73%)	0.80
ACE or ARB	254 (65%)	242 (61%)	0.28
Clopidogrel	101 (27%)	105 (28%)	0.74
Warfarin	45 (12%)	32 (8.5%)	0.118
Aspirin or warfarin	334 (86%)	351 (90%)	0.079
Aspirin, warfarin or clopidogrel	345 (89%)	364 (93%)	0.044
Diabetes medication			
Insulin	41 (11%)	43 (11%)	0.85
Oral hypoglycemic	70 (19%)	114 (30%)	P<0.001

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* Median, 25th and 75th percentiles are reported for all continuous variables.

eTable 4
Baseline Characteristics of Patients Who Prematurely Discontinued High-Dose Vitamins by Treatment Group

	Placebo (N=390)	High-Dose Vitamins (N=394)	P-value
Multivitamin**	171 (45%)	155 (41%)	0.22
Other vitamins/minerals**	190 (50%)	186 (49%)	0.74
Herbal products	136 (36%)	116 (31%)	0.099
Laboratory Examinations			
Glucose (mg/dL)	103.0 (93.0, 120.0)	103.0 (93.0, 127.0)	0.47
Creatinine (mg/dL)	1.1 (0.9, 1.2)	1.1 (0.9, 1.2)	0.55
Total cholesterol (mg/dL)	166.0 (142.0, 200.0)	166.0 (143.0, 198.0)	0.74
HDL (mg/dL)	42.0 (36.0, 50.0)	43.0 (36.0, 52.0)	0.139
LDL (mg/dL)	91.0 (66.0, 120.0)	90.0 (68.0, 116.0)	0.63
Triglycerides (mg/dL)	144.0 (97.0, 200.0)	142.0 (101.0, 203.0)	0.88

* Median, 25th and 75th percentiles are reported for all continuous variables.
** * Participants were taking at baseline / prior to initiation of the study.

Adverse Events Reported During the Trial

The following tables (eTable 5 and eTable 6) provide a detailed summary of adverse events reported in the trial. The serious and non-serious adverse events are individually listed, grouped by the body system involved (from the MEDRA coding system), and compared according to the randomized vitamin groups (active high-dose vitamins vs. placebo).

eTable 5
Serious Adverse Events by Vitamin Arm

Events	Placebo (N=855)	High-Dose Vitamins (N=853)	95% CI for Difference*
Total	103 (12%)	124 (15%)	(-0.7, 5.7)
Cardiac Disorders	33 (3.9%)	39 (4.6%)	(-1.2, 2.6)
Gastrointestinal Disorders	12 (1.4%)	12 (1.4%)	(-1.1, 1.1)
General Disorders and Administration Site Conditions	10 (1.2%)	13 (1.5%)	(-0.7, 1.4)
Hepatobiliary Disorders	2 (0.2%)	3 (0.4%)	(-4.7, 4.9)*
Infections and Infestations	18 (2.1%)	16 (1.9%)	(-1.6, 1.1)
Injury, Poisoning and Procedural Complications	7 (0.8%)	7 (0.8%)	(-4.8, 4.8)*
Investigations	2 (0.2%)	4 (0.5%)	(-4.5, 5.0)*
Metabolism and Nutrition Disorders	3 (0.4%)	1 (0.1%)	(-5.0, 4.6)*
Musculoskeletal and Connective Tissue Disorders	2 (0.2%)	3 (0.4%)	(-4.7, 4.9)*
Neoplasms	4 (0.5%)	7 (0.8%)	(-4.4, 5.1)*
Nervous System Disorders	7 (0.8%)	11 (1.3%)	(-4.3, 5.3)*
Psychiatric Disorders	1 (0.1%)	3 (0.4%)	(-4.5, 5.0)*
Renal and Urinary Disorders	4 (0.5%)	6 (0.7%)	(-4.5, 5.0)*
Respiratory, Thoracic and Mediastinal Disorders	15 (1.8%)	18 (2.1%)	(-0.9, 1.7)
Skin and Subcutaneous Tissue Disorders	0	1 (0.1%)	(-4.7, 4.9)*
Surgical and Medical Procedures	1 (0.1%)	0	(-4.9, 4.7)*
Vascular Disorders	5 (0.6%)	6 (0.7%)	(-4.7, 4.9)*

* Exact 95% CI values are reported where marked with an asterisk.
The other rows contain asymptotic 95% CI values.

eTable 6
Non-Serious Adverse Events by Vitamin Arm

Events	Placebo (N=855)	High-Dose Vitamins (N=853)	95% CI for Difference*
Total	585 (68%)	569 (67%)	(-6.2, 2.7)
Blood and Lymphatic System Disorders	39 (4.6%)	46 (5.4%)	(-1.2, 2.9)
Cardiac Disorders	53 (6.2%)	48 (5.6%)	(-2.8, 1.7)
Ear and Labyrinth Disorders	1 (0.1%)	5 (0.6%)	(-4.3, 5.3)*
Eye Disorders	6 (0.7%)	8 (0.9%)	(-4.5, 5.0)*
Gastrointestinal Disorders	124 (15%)	105 (12%)	(-5.4, 1.0)
General Disorders and Administration Site Conditions	100 (12%)	120 (14%)	(-0.8, 5.5)
Hepatobiliary Disorders	1 (0.1%)	2 (0.2%)	(-4.7, 4.9)*
Immune System Disorders	4 (0.5%)	1 (0.1%)	(-5.1, 4.4)*
Infections and Infestations	105 (12%)	110 (13%)	(-2.5, 3.8)
Injury, Poisoning and Procedural Complications	31 (3.6%)	23 (2.7%)	(-2.6, 0.7)
Investigations	208 (24%)	198 (23%)	(-5.2, 2.9)
Metabolism and Nutrition Disorders	240 (28%)	232 (27%)	(-5.1, 3.4)
Musculoskeletal and Connective Tissue Disorders	62 (7.3%)	69 (8.1%)	(-1.7, 3.4)
Neoplasms	7 (0.8%)	5 (0.6%)	(-5.0, 4.6)*
Nervous System Disorders	54 (6.3%)	61 (7.2%)	(-1.5, 3.2)
Psychiatric Disorders	8 (0.9%)	20 (2.3%)	(0.2, 2.6)
Renal and Urinary Disorders	75 (8.8%)	76 (8.9%)	(-2.6, 2.8)
Reproductive System and Breast Disorders	8 (0.9%)	6 (0.7%)	(-5.0, 4.6)*
Respiratory, Thoracic and Mediastinal Disorders	88 (10%)	66 (7.7%)	(-5.3, 0.2)
Skin and Subcutaneous Tissue Disorders	24 (2.8%)	20 (2.3%)	(-2.0, 1.0)
Vascular Disorders	37 (4.3%)	39 (4.6%)	(-1.7, 2.2)

* Exact 95% CI values are reported where marked with an asterisk.
The other rows contain asymptotic 95% CI values.

eTable 7
Comparison of TACT vitamin regimen with Centrum Silver

Centrum® Silver® Adults 50+				**TACT High Dose Regimen**		
Serving Size 1 Tablet				*Serving Size 6 Tablets*		
Each Tablet Contains		% Daily Value		Each Tablet Contains		% Daily Value
Vitamin A	2,500 IU (40% as Beta-Carotene)	50%		Vitamin A (as fish liver oil and beta-carotene)	25,000 IU	500%
Vitamin C	60 mg	100%		Vitamin C (as calcium ascorbate, magnesium ascorbate and potassium ascorbate)	1,200 mg	2000%
Vitamin D	500 IU	125%		Vitamin D_3 (as cholecalciferol)	100 IU	25%
Vitamin E	50 IU	167%		Vitamin E (as d-alpha tocopheryl succinate and d-alpha tocopheryl acetate)	400 IU	1333%
Vitamin K	30 mcg	38%		Vitamin K_1 (as phytonadione)	60 mcg	75%
Thiamin	1.5 mg	100%		Thiamin (vitamin B_1) (as thiamin mononitrate)	100 mg	6667%
Riboflavin	1.7 mg	100%				
Niacin	20 mg	100%		Niacin (as niacinamide and niacin)	200 mg	1000%
Vitamin B6	3 mg	150%		Vitamin B_6 (as pyridoxine hydrochloride)	50 mg	2500%
Folic Acid	400 mcg	100%		Folate (as folic acid)	800 mcg	200%
Vitamin B12	25 mcg	417%		Vitamin B_{12} (as cyanocobalamin)	100 mcg	1667%
Biotin	30 mcg	10%		Biotin	300 mcg	100%
Pantothenic Acid	10 mg	100%		Pantothenic acid (as d-calcium pantothenate)	400 mg	4000%
Calcium	220 mg	22%		Calcium (as calcium citrate and calcium ascorbate)	500 mg	50%
Phosphorus	20 mg	2%				
Iodine	150 mcg	100%		Iodine (from kelp)	150 mcg	100%
Magnesium	50 mg	13%		Magnesium (as magnesium aspartate, ascorbate and amino acid chelate)	500 mg	125%
Zinc	11 mg	73%		Zinc (as zinc amino acid chelate)	20 mg	133%
Selenium	55 mcg	79%		Selenium (as selenium amino acid chelate)	200 mcg	286%

Copper	0.5 mg	25%	Copper (as copper amino acid chelate)	2 mg	100%
Manganese	2.3 mg	115%	Manganese (as manganese amino acid chelate)	20 mg	400%
Chromium	45 mcg	38%	Chromium (as chromium polynicotinate)	200 mcg	167%
Molybdenum	45 mcg	60%	Molybdenum (as molybdenum amino acid chelate)	150 mcg	200%
Chloride	72 mg	2%			
Potassium	80 mg	2%	Potassium (as potassium aspartate and potassium ascorbate)	99 mg	3%
Boron	150 mcg	*	Boron (as boron aspartate and boron citrate)	2 mg	*
Nickel	5 mcg	*			
Silicon	2 mg	*			
Vanadium	10 mcg	*	Vanadium (as vanadyl sulfate)	39 mcg	*
Lutein	250 mcg	*			
Lycopene	300 mcg	*			
			Citrus Bioflavonoids	100 mg	*
			Choline (as choline bitartrate)	150 mg	*
			Inositol	50 mg	*
			PABA (as para-amino benzoic acid)	50 mg	*

* Daily Value not established.
Suggested use: Adults – Take one tablet daily with food.

on Centrum Silver, but not on TACT Vitamins